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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,501	12/17/2001	Guido Henning	Le A 35 012	4394

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Jeffrey M. Greenman
Vice President, Patents and licensing
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

EXAMINER	
WALLENHORST, MAUREEN	
ART UNIT	**PAPER NUMBER**
1743	

DATE MAILED: 08/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/023,501	HENNING ET AL.	
	Examiner	Art Unit	
	Maureen M. Wallenhorst	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/7/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Applicants are informed that Examiner Maureen Wallenhorst has taken over examination of the instant application.

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

3. Claims 1-5 and 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

On line 7 of claim 1, the phrase "specifically bind to at least two molecular markers" is indefinite since it is not clear whether these markers are the same as the at least two molecular markers that were selected in the first step of the method. On line 9 of claim 1, the phrase "of a tissue section" is indefinite since the claim did not previously recite that the sample being analyzed was a tissue section. Rather, claim 1 previously recited that the sample being analyzed was a cell or tissue sample.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-2, 4-5 and 8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3 and 4 of copending Application No. 10/022,618. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are broader than those of the 10/022,618 application in that the instant claims recite cancer cells and their precursors, whereas the claims of the '618 application recite cancer cells and their precursors "in uterine cervical smears". The instant claims are broader than the claims of the '618 application and are thus anticipated by the '618 application. See In re Goodman.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Rao et al (see the journal articles entitled "Single Cell Multiple Biomarker Analysis in Archival Breast Fine-Needle Aspiration Specimens: Quantitative Fluorescence Image Analysis of DNA Content, p53 and G-actin as Breast Cancer Biomarkers", submitted in the IDS filed on July 8, 2002).

Rao et al teach of a method for evaluating breast legions for cancerous cells. The method of Rao et al involves staining markers such as p53, G-actin and DNA content in breast legion samples with a stain. In the abstract of the article, Rao et al specifically teach QF image analysis of multiple biomarkers (p53, G-actin and DNA content) on a single cell basis. With respect to the staining, Rao et al teach at page 1028 that immunofluorescent labeling takes place by using a Code-On automatic stainer. Page 1030 further describes the staining as distinctive in that G-actin stains more intensively in cytoplasm, whereas p53 is slightly stronger in the nuclei of tumor cells. After staining, the samples are scanned by an automated image analysis system and biomarkers are detected. Cellular portions of the samples are imaged and measured, and the values are automatically stored in a database. See page 1028. The data is analyzed quantitatively and qualitatively, and the results are converted into positive-negative schema. The data analyses are carried out using a software program (i.e. Microsoft Excel program). The image analysis system is considered to be an automatic information processing system that is linked to a diagnostic expert system. The software program taught by Rao et al is taken to be a diagnostic expert system because of its ability to convert the quantitative values into positive-negative schema (i.e. convert the data into a diagnosis of a disease state). See pages 1028 and 1030 of Rao et al. Rao et al further performed the method using multiple markers, such as the combination of G-actin and DNA content. The article states that none of the benign cases were

positive for G-actin and DNA simultaneously, and that none of the cancer cases were negative for G-actin and DNA content simultaneously. Thus, the measurement of the two biomarkers took place simultaneously as a mixture of biomarkers. The article teaches that using multiple markers provides a powerful tool for breast cancer detection. See page 1031. With respect to claim 5, Rao et al's teaching of the detection of cancerous cells in breast legions meets the limitation of detecting tumors in the mammary gland.

9. Claims 1, 3-5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by McNamara et al.

McNamara et al teach of a method for analyzing cells for the detection of cancerous cells, such as those found in breast cancer, ovarian and/or endometrial cancer and prostate cancer. The method of McNamara et al involves staining a cell sample with multiple stains including immunohistochemical, histological and DNA ploidy stains. Each immunohistochemical stain is coupled with a primary antibody known to bind with their respective cytological markers and is used in the diagnosis of diseases, such as cancer. Specifically, McNamara et al teach antibodies to p53, Her-2/neu, EGFR, Ki-67 and Bcl-2 (see col. 40, lines 25-67). For breast cancer, McNamara et al teach using PR, Her-2/neu, p53, CD31 and Ki-67. For prostate cancer, McNamara et al teach using Ki-67, CD31 and p53 (see col. 41, lines 28-40). At col. 41, lines 55-64, McNamara et al teach that a clinician can simultaneously detect multiple cytological markers (p53, Her-2/neu, Ki-67) allowing a more accurate diagnosis. After staining of the samples, spectral imaging is performed and the data is collected using a SPECRTACUBE™ (col. 36, line 64-col. 37, line 23). In analyzing the results of the data collected, McNamara et al teach using spectral and spatial data. The spectral data is displayed as a useful image for the user. The

spatial-spectral correlation of the spectrum image provides data about various types of cells that may appear similar to the naked eye. Thus, in addition to the image data, the cells can also be differentiated.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Rao et al or McNamara et al in view of Bacus et al (US Patent no. 5,109,429). For a teaching of Rao et al and McNamara et al, see previous paragraphs in this Office action.

The disclosures of both Rao et al and McNamara et al fail to teach of a kit having the necessary reagents therein for carrying out the method for detecting cancerous cells.

Bacus et al teach of a kit for analyzing biological specimens for cancer diagnosis and/or prognosis. The kit of Bacus et al comprises slides, one or more bottles of staining reagent, auxiliary agents, such as sulfonating agents and buffers, instructions for the operator and a

reference area for calibration. Bacus et al teach that the kit provides an easy and inexpensive means for detecting minute alterations in specimen cells.

Based upon the combination of either Rao et al or McNamara et al and Bacus et al, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the components needed to carry out the methods taught by Rao et al and McNamara et al into a kit so as to allow a user to have all of the supplies needed for the easy detection of cancer cells in a convenient package.

13. Applicant's arguments filed June 7, 2006 have been fully considered but they are not persuasive.

Applicants argue the rejection of the claims under 35 USC 102(b) as being anticipated by Rao et al by stating that the presently claimed method requires the use of at least two molecular markers that individually do not achieve sufficient specificity with regard to detecting cancer, and that the markers proposed by Rao et al do not meet this requirement since Rao et al teach that G-actin alone is able to detect differentiated cancer, and DNA content is not unique to the detection of cancer. In response to these arguments, it is first noted that Rao et al only teach that G-actin can individually distinguish between well-differentiated cancer and poorly differentiated cancer. In other words, Rao et al teach that G-actin can be correlated with the degree of differentiation in already existing cancer, not that G-actin can individually distinguish between cancerous and non-cancerous cells or tissue. Rao et al clearly teach that a combination of three markers is needed to detect cancer with specificity since each marker is specific for detecting a different stage of carcinogenesis. See the first full paragraph on page 1028 of Rao et al where G-actin is described as a cancer differentiation marker, p53 is described as a tumor suppressor gene

used for detecting the early stages of cancer, and DNA content is described as detecting late stages of caner and tumor progression. The use of only one of these markers would not achieve the specificity that is provided by the combination of all three of G-actin, p53 and DNA content. If only one of these markers were sufficiently specific to detect cancer by itself, Rao et al would have used only one of the markers since the detection and analysis of only one marker is much simpler that the combined detection and analysis of three markers. With regards to DNA content, Applicants' argument concerning DNA content being used for other purposes such as the characterization of myocardial hypertrophy is not persuasive since Rao et al clearly teach that DNA content can also be used to detect cancer in conjunction with other markers. See the first full paragraph on page 1028 of Rao et al. However, its used alone as a cancer detection agent is not feasible since it does not have the required specificity to alone detect cancer, as disclosed by Rao et al.

Applicants also argue that Rao et al do not teach or suggest the step of combining and accrediting the signal intensities of the detected markers in the cell or tissue sample since Figure 3 of Rao et al separately analyzes the detected signals of G-actin, p53 and DNA content. In response to this argument, it is noted that Rao et al do simultaneously measure the fluorescence of the three markers G-actin, p53 and DNA content using a QFIA image analysis system. See the paragraph entitled "QFIA for Biomarkers" on page 1028 of Rao et al. This analysis system analyzes all of the signal intensities for each of the markers simultaneously as in the instant invention. Figure 3 of Rao et al simply breaks down the percentage of the combined signal intensity that is due to each of the individual markers.

Applicants argue that Rao et al do not teach or suggest the step of automatically processing the signal intensities into image information and consolidating the information into a proposed diagnosis using a linked diagnostic expert system since there is no automation involved in the analysis of the quantitative and qualitative fluorescence intensity data. This argument is not persuasive since Rao et al teach that all quantitative and qualitative data analysis, as described in the last paragraph on page 1028, page 1029 and the first two lines of page 1030, is performed using a Microsoft Excel program, and the use of such a program runs automatically on a computer.

Applicants argue the rejection of the claims under 35 USC 102(b) as being anticipated by McNamara et al by stating that McNamara et al fail to teach of combining and accrediting the signal intensities of the detected markers since McNamara et al use overlaid or overlapping separately-detected staining images to analyze the signal intensities, which does not constitute combining and accrediting signal intensities as used in the instant invention. This argument is not found persuasive since the overlapping image of all the staining intensities from each of the markers used by McNamara et al does constitute a step of combining all of the signal intensities from each stain used. In addition, lines 18-26 in column 54 of McNamara et al states that a pathologist can use the classification image, obtained from the combination of the stain signal intensities on the overlaid image, to evaluate the presence/absence/aggression level/diagnosis and/or prognosis of cancer cells. This step is equivalent to accrediting the combined signal intensities to a diagnosis of cancer/non-cancer in a cell or tissue sample, as recited in the instant claims.

Applicants argue that McNamara et al fail to teach the step of automatically processing the signal intensities into image information and consolidating the information into a proposed diagnosis using a linked diagnostic expert system. In response to this argument, it is noted that this limitation is recited in instant claim 2, which is not rejected by the reference to McNamara et al. However, McNamara et al do teach of using spectral algorithms to analyze the spectral data of the stained cells, and two-dimensional image processing algorithms to analyze the spatial data of the stained cells, and algorithms are usually performed automatically on a computer.

Applicants argue the rejection of claim 7 using the references to either Rao et al or McNamara et al and Bacus et al by stating that Bacus et al do not cure the deficiencies of the primary references since Bacus et al do not teach using at least two markers that individually do not achieve sufficient specificity with regard to detecting cancer cells, combining and accrediting the detected signal intensities of the markers, or automatically processing the signal intensities into image information and consolidating the information into a proposed diagnosis using a linked diagnostic expert system. In response to this argument, it is noted that if the secondary reference to Bacus et al taught all of these limitations, then it would have been applied against the claims under 35 USC 102. However, Bacus et al was used as a secondary reference in a rejection under 35 USC 103 to show the obviousness of incorporating all of the reagents and other components needed to perform the methods of Rao et al and McNamara et al into a kit so as to allow the easy, quick and efficient performance of the methods by having all of the required reagents and components in a packaged form ready-to-use.

The Examiner notes Applicants' request to hold remarks regarding the obviousness-type double patenting rejection in abeyance until claims are allowable over the cited prior art of record.

Applicants are informed that the U.S. references to Rutenburg et al and McGlynn et al on the IDS filed Augsust 7, 2006 have been crossed out since these references were already considered in the IDS filed on August 5, 2002. The references to Bacus et al and Barnhill et al have been crossed out since these references were already considered and made of record on the PTO-892 form attached to the Office action mailed on September 17, 2004.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maureen M. Wallenhorst whose telephone number is 571-272-1266. The examiner can normally be reached on Monday-Thursday from 6:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden, can be reached on 571-272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maureen M. Wallenhorst
Primary Examiner
Art Unit 1743

mmw

August 11, 2006

Maureen M. Wallenhorst
MAUREEN M. WALLENHORST
PRIMARY EXAMINER
GROUP 1700